Rejection with respect to U.S. Patent 5,837,233

Claims 1-10, 12-16 and 18-20 stand rejected under 35 USC § 102(b) or alternatively under 35 USC § 103(a) as obvious over Granger (U.S. Patent 5,837,233). The basis of the rejection is new. The Office Action infers from a sentence starting on Line 64 of Column 5 that Granger teaches more than one dose of alloactivated cells to a tumor site.

Applicant respectfully disagrees. Nowhere does the Granger patent teach or fairly suggest that two doses are to be administered *to a single patient.*

The passage referred to instructs the reader to use the compositions of the Granger patent *in accordance with conventional prudent formulating practices* for typical medicines used for treating cancer. Conventional cancer medicines are small-molecule drugs *given by daily administration or ongoing infusion.* In some instances, it may make sense to start treatment with a small-molecule drug at a particular dose level, and then adjust the dose level for subsequent doses being given as a matter of course.

The Granger technology is clearly not such an instance. The pharmaceutical composition is not a small molecule drug, it is a cell preparation produced by way of an expensive tissue-culture procedure. It must be prepared anew and afresh for each patient; administration to glioma patients occurs during a complex and invasive surgical procedure that involves opening up the skull cavity; and the efficacy of the treatment is not necessarily evident for a number of weeks. It is not reasonable to infer from this passage that the patient should have their skull cavity opened up on a daily or weekly basis in order to fine-tune the dosage level.

To be fair, the passage referred to can only be interpreted within the context of the invention described and claimed in the patent — which produces a much different meaning. The passage does not indicate that sequential administrations of MLC cells should be made *to the same patient.* What it does indicate is that when the proper dose is not known, the clinician should err on the side of caution and administer *a dosage near the lower end of the useful range.* Depending on the efficacy of treatment and side effect profile, the clinician may

then decide to treat *subsequent patients* with an increased or decreased dosage, as indicated from the observed response in the initial patients.

In fact, this is how Granger conducted the clinical study in the brain cancer patients (Example 1). Nine patients were admitted to the study, and divided into three different groups to receive three different dosage levels, *each patient receiving a single dose.* Partitioning of the patients into different groups in the manner referred to in the previous paragraph allowed Granger to make conclusions about appropriate doses. Just following the passage quoted in the Office Action, the patent continues: *In general, . . . a unit dosage for direct implant comprises from about 2×10^9 to about 6×10^9 MLCs. For instance, it has been discovered that in the treatment of brain tumors, the upper limit of cells that can be implanted is about 6×10^9.*

The passage referred to in Col. 5 merely counsels the practicing clinician to err on the side of caution when applying the invention to a new type of cancer, or using a slightly altered MLC formulation. In fact, this is exactly what Granger does when he takes his experience from the brain cancer trial, and applies it to other cancers. The first melanoma patients are treated at a dose of 2×10^9 cells (Example 2), and the first pancreatic cancer patients are treated at a dose of 2×10^9 cells (Example 3) — which is low to mid range for what was determined to be the window of safety when the invention was applied to brain cancer — a good starting place from which to empirically determine the dose that provides optimum safety and efficacy.

To the extent that there is any ambiguity as to how to apply the passage referred to in the Office Action, the reader must interpret the passage in light of what is taught in the rest of the patent disclosure. Following the rationale put forward by the Office Action, evidence of failure of treatment would lead the clinician to "increase the dosage" give to the patient — or at least administer a second dose at some level. Yet this was never reported in any of the studies described in the Granger patent disclosure.

Referring to Figure 2 of the Granger patent, the kinetics of tumor size can be seen following treatment. There is a considerable drop in the apparent tumor volume between the

time of original assessment (the first time point in each series), and the time of first assessment after surgery. This is due to the fact that the tumor is debulked at the time the MLCs are implanted (Line 66, Col. 10 ff.). The first post-surgery MRI is taken after inflammation subsides. Evidence of reduction in apparent tumor size would come from decline in volume between the first post-surgery image and subsequent images along the time course.

From the data shown, the patients Lundy, Powers, Jacobson and Cane show a reduction in apparent tumor volume. By this criterion, the other five patients in the study showed no effect of the treatment. The other clinical data provided in the study, of course, is survival (Figure 1), with only 2 of the 9 patients surviving beyond the period of the study. *Yet not one of the patients were ever given a second dose* of any size in an attempt to generate a more vigorous response — even when there was no apparent reduction in tumor volume. Of course, the usual prognosis for glioblastoma is extremely grave, and the increased survival that was observed in a substantial proportion of the treated patients represents a major advance. But all the evidence in the patent disclosure indicates that Granger thought that a single dose was sufficient to generate a complete response. Since the patients apparently were responding to the tumor as best they could, there is no motivation for the reader to undertake the invasive procedure necessary to apply a second dose.

The passage referred to in the Office Action starting at Line 64, Col. 10 must be interpreted with this intent — meaning that it counsels clinicians only in terms of adjusting dose between different patients — and is silent about giving multiple sequential cell populations to the same patient.

Thus, a fair interpretation of the Granger patent is sufficient to establish that this reference is not patent-defeating for any of the pending claims under 35 USC § 102 or § 103. Furthermore, many of the dependent claims are also patentable over the Granger patent because they recite additional limitations that are not taught or suggested by Granger.

Claims 2, 3, 4, and 14 are patentable over the Granger patent, because these claims require that the second dose be administered *even when there is information verifying that the patient has been stimulated to form an immune response by the first injection alone.* To be consistent with the logic presented in the Office Action, there would be no motivation to bear the risk and expense of administering a second implant into the tumor if the patient was already responding to the first implant.

Claim 6 is patentable over the Granger patent, because Granger does not teach or suggest alloactivating the lymphocytes using leukocytes from a third-party donor.

Claim 7 is patentable over the Granger patent, because the second dose is administered before the clinician would be able to fairly assess the effect of the first dose. As shown in Figure 2 of the Granger patent, the first post-treatment MRI image is obtained several weeks after the procedure when inflammation has subsided. A meaningful difference will appear in individual patients only after a suitable interval, at least another 6 weeks. Thus, the patients in the Granger study were subject to their second MRI image at about 10 weeks post therapy. Before that time, the clinician would have no MRI data to indicate a reduction in tumor size. Claim 7 requires that the second cell population be implanted before the 8 week point, *even in the absence of any information on the effect of the first implant.*

New Claims 21 and 22 are patentable over the Granger patent, because they require that the surgeon *leave tumor in the patient* after the first administration, even though it is sufficiently accessible to allow the first cell population to be implanted. Granger teaches that the tumor should be removed at the time of the original implant(Line 14, Col. 8). Before the invention described in the present application, it would be counterintuitive to ask a surgeon to leave tumor cells behind, during a procedure being conducted specifically for the purpose of treating the cancer. But the present invention teaches that leaving tumor at the treatment site between the two doses can be beneficial when implanted cell populations are used to induce a host response against the tumor. This feature is explicitly required in Claims 21 and 22.

For all these reasons, withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 102(f)

Claims 1-8, 12-14 and 18-20 stand rejected under 35 USC § 102(f) because the applicant is alleged not to be the inventor of the claimed subject matter. This is a new rejection. The Office Action cites PCT publication WO 98/16238 (which has the same description as U.S. Patent 6,207,147, issued March 27, 2001).

The invention described and claimed in the cited reference differs from the present invention in a number of ways. In the present invention, neither the first nor the second cell population contain tumor cells. Instead, they are both implanted into the tumor bed, where it has been discovered that there is sufficient tumor antigen to stimulate a response against the tumor. Two implant procedures are required, unlike the distal-site vaccination strategy of the cited reference. The present application teaches that the double procedure is worthwhile because the sequential implant has important and valuable synergistic effects.

Withdrawal of this rejection is respectfully requested.

Rejection with respect to Feldhaus and Haugland

Claims 11 and 17 stand rejected under 35 USC § 103(a) as being unpatentable over the Granger patent (U.S. 5,837,233), in view of U.S. Patent 5,759, 805 (Feldhaus et al.) and *Handbook of Fluorescent Probes and Research Chemicals,* R.P. Haugland, 5th ed. Molecular Probes Inc., 1992.

Applicants respectfully disagree. The Granger patent does not teach or fairly suggest the administration of multiple sequential implants to a single patient, as already explained. Upon removal of Granger as a reference, the rejection no longer applies.

Furthermore, the supplemental references do not supply all the limitations of the claim. Feldhaus et al. relates to the promoter region that drives transcription of the CD69 gene early in lymphocyte activation. Haugland is a general textbook and catalog relating to the use of fluorescent reagents to detect cellular activation. Neither of these references relates to a key limitation in feature iii) of Claims 11 and 17, which is the requirement for the

alloactivated lymphocytes to be harvested from culture *at about the time of initial alloactivation.*

Withdrawal of this rejection is respectfully requested.

Rejection with respect to Kruse et al.

Claims 1, 2, 6-8 and 12 stand rejected under 35 USC § 103(a) as anticipated by Kruse et al. (J. Neuro-Oncology 19:161, 1994).

This publication was been cited against this application in the pending Office Action for the first time. However, it is cumulative with the two references by Kruse et al. cited in the previous Office Action, which were addressed in the previous Amendment, which in turn led to withdrawal of the rejection. The reference compares the effect of a combination of cytotoxic T lymphocytes (CTLs) generated from different strains on the treatment of rat 9L gliosarcoma in an inbred rat strain, in comparison with untreated controls.

Like the other Kruse et al. references addressed previously, the technology of this newly cited reference is fundamentally different from that of the invention claimed in this patent application. Specifically, the CTLs of the reference are referred to as CTLs because they are designed to have *direct cytolytic activity* against the tumor. The CTLs are co-administered with recombinant IL-2 to maintain their CTL phenotype (Page 163, Col. 2 ¶ 2). In contrast, the implant cells of the claimed invention are designed *as stimulators to induce a response by the host.* This difference was explained in further detail in the previous Amendment, and the arguments can be adapted *mutatis mutandis* to address this new rejection.

The Patent Office has acknowledged the differences between the technology described by Kruse and her colleagues, and the technology for implanting alloactivated cells into a tumor bed to elicit a host response. Specifically, the Office has issued two patents to the implant technology by Granger: U.S. 5,837,233 (issued November 17, 1998) and U.S. 6,136,306 (issued October 24, 2000). In allowing both of these patents, the Examiner gave

careful and thorough consideration to all the publications by Kruse et al. of record in this application, including the cited reference in J. Neuro-Oncology 19:161, 1994.

The Examiner of the Granger patents agreed that the implant technology is distinguishable from the technology of Kruse et al. by a number of criteria, including the following:

1. The implant cells have the ability to stimulate a response by the host against the tumor;
2. The implant cells are harvested from culture during the initial stage of activation;
3. When administered in or around the site of the tumor, the implant cells can be immunogenic for an anti-tumor immunological response; and
4. The cells can be used for treating tumors in sites that are not immunologically privileged, such as melanoma, pancreatic cancer, liver cancer, colon cancer prostate cancer, and breast cancer.

Any one of these criteria when presented as a claim limitation was considered sufficient to render the claim patentable under 35 USC §§ 102 or 103. The Granger patents were issued accordingly.

All of the claims pending in the present application also recite at least one of these limitations:

- Limitation 1 appears in Claim 1 and its dependents
- Limitation 2 appears in Claim 11, 17, and their dependents
- Limitation 3 appears in Claim 4, 13, and their dependents
- Limitation 4 appears in Claim 12, 18, and their dependents

Since this covers all pending claims in this application, the claimed invention is patentable with respect to all the work by Kruse et al. of record in this application, under both 35 USC §§ 102 and 103.

Applicant explained in the last Amendment why the references of Kruse et al. cannot properly be combined with the Granger patents.

Withdrawal of this rejection is respectfully requested.

Request for Interview

Applicant requests that all outstanding rejections be reconsidered and withdrawn in light of this submission. The application is believed to be in condition for allowance, and rapid issuance of a Notice of Allowance is respectfully requested.

If upon consideration of this paper the Examiner does not consider that the application is in condition for allowance, applicant hereby requests an in-person interview between the Examiner and the undersigned, to be scheduled if possible within a month of this submission.

Should the Patent Office determine that a further extension of time or other relief is required for further consideration of this application, applicant hereby petitions for such relief and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of this document to the Credit Card indicated on accompanying PTO-2038.

Respectfully submitted,

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